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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/480,389	01/11/2000	Bruce M. Boman	CATX-N	4258

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/480,389	BOMAN, BRUCE M.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28,32-35,37-44,55-57 and 59-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28,32-35,37-44,55-57 and 59-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed March 3, 2004 was entered. Claims 62-80 were added.

Claims 24-28, 32-35, 37-44, 55-57 and 59-80 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejection of claims 24-28, 32-35, 37, 39, 43, 55-57, 59-61 under 35 U.S.C. 103(a) as being unpatentable over Vogelstein (U.S. 5,650,281; issued July 22, 1997; effective filing date Jan. 4, 1990) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992) is withdrawn in view of applicant's persuasive arguments.

5. The rejection of claims 24-28, 32-35, 37-40, 43, 44, 55-57, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markowitz (U.S. 5,866,323; issued Feb. 2, 1999; effective filing date May 22, 1995) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992) is withdrawn in view of applicant's persuasive arguments.

6. The rejection of claims 24-28, 32-35, 37-41, 43, 44, 55-57, 59-61 under 35 U.S.C. 103(a) as being unpatentable over Liskay (U.S. 6,165,713; issued Dec. 26, 2000; effective filing date

Dec. 9, 1994) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992) is withdrawn in view of applicant's persuasive arguments.

7. The rejection of claims 24-28, 32-35, 37-40, 43, 44, 55-57, 59-61 under 35 U.S.C. 103(a) as being unpatentable over Tavtigian (U.S. 6,124,104; issued Sep. 26, 2000; effective filing date Apr. 29, 1996) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992) is withdrawn in view of applicant's persuasive arguments.

8. The rejection of claims 24-28, 32-35, 37-40, 43, 44, 55-57, 59-61 under 35 U.S.C. 103(a) as being unpatentable over Albertsen (U.S. 6,413,727; issued Jul. 2, 2002; effective filing date Aug. 8, 1991) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992) is withdrawn in view of applicant's persuasive arguments.

Claim Rejections Maintained:

9. The rejection of claims 24-28, 32-35, 37-44, 55-57 and 59-61 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons of record and is applied to new claims 62-80. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The basis for this rejection is that applicant not in possession of the claimed methods at the time of filing, because the disclosure fails to describe the genus of disease or disease-susceptibility traits that are "known" to be associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein normally expressed by one of two or more subject genes.

Applicant's arguments have been carefully considered but are unpersuasive. Applicant has not shown where in the specification support can be found for what constitutes "knowing" that disease or disease-susceptibility trait is associated with a germ-line mutation that causes an about 50% decrease in the level of wild-type protein. It appears that one would have to perform the claimed assay in order to "know" that a disease or disease-susceptibility trait is associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein. Therefore, the rejection is maintained.

New Grounds of Rejection:

10. Claims 24-28, 32-35, 43, 44, 55-57, 61, 73, 74, 75, 79, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pece (Pece, N. et al. J. Clin. Invest. 100(10): 2568-2579, 1997, November; cited in IDS) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992).

Pece teaches a method of measuring wild-type endoglin protein levels using quantitative flow cytometry where the difference in endoglin levels between a newborn from a family that carries a mutation that causes hemorrhagic telangiectasia type I (HHT1) and normal shows that the newborn from the family with HHT1 express 46% surface endoglin relative to the normal

controls, where the expression of α5β1 integrin and CD31 are also measured to indicate a specific reduction in endoglin levels (page 2573, 1st col.). Pece also teaches quantitative Western blots that show that patient samples have 50% of normal levels of endoglin homodimers (page 2573, , 2nd col.). Pece teaches that normal endoglin is expressed at half-levels relative to control in activated monocyte samples from HHT patients (page 2574, 2nd col.). Pece concludes that reduces expression of functional endoglin is a defect in HHT1Page 2577, 1st col).

Pece fails to explicitly teach making a ratio of protein levels of one subject gene to that of another subject gene. However, Pece does support conclusions of a reduction in protein expression to 50% of normal by using methods where the expression levels of another gene are examined (α5β1 integrin and CD31). Also, Nozawa teaches a method for the quantification of protein levels by relating the measured amount to amount of a second protein (see col. 3, line 40 – col. 4, line 5; claim 1; col. 7, lines 24-36). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed methods, because Pece teaches that endoglin levels are reduced to 50% of normal in those with a predisposition for HHT1 or those actually affected by HHT1 and because methods for specifically quantitating antigens of interest by relating the amount of the detected antigen to the amount of a second antigen is known in the art. Nozawa teaches the motivation for use of such quantification methods by describing many of the problems that may occur when attempting to associate the detection of an antigen with a disease state (see col. 1, line 32 – col. 3, line 39).

11. Claims 24-28, 32-35, 37-39, 43, 44, 55-57, 61, 73-77, 79, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glendening (Glendening, J. M. et al., Cancer Res. 55:

5531-5535, 1995) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992).

Glendening teaches that deletion of a single copy of p16INK4 appears to be enough to initiate or drive the development of melanoma (page 5535, 1st col). Glendening teaches that germline mutations with in the p16INK4 gene have been described for families where melanoma is common (see abstract). Glendening teaches that in cells showing p16INK4 mutations, p16INK4 protein is still expressed indicating that there is haploinsufficiency (see abstract and page 5532, 2nd col).

Glendening fails to teach methods where normal cells from patients are used for measurements of p16INK4 protein levels and also fails to explicitily teach making a ratio of protein levels of one subject gene to that of another subject gene. However, Glendening does teach that haploinsufficiency of p16INK4 does appear to be a factor in the development of melanoma and does teach that it is known in the art that germline mutations of p16INK4 exist. Also, Nozawa teaches a method for the quantification of protein levels by relating the measured amount to amount of a second protein (see col. 3, line 40 – col. 4, line 5; claim 1; col. 7, lines 24-36). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed methods, because Glendening teaches that haploinsufficiency of p16INK4 appears to be a factor in the development of melanoma and because methods for specifically quantitating antigens of interest by relating the amount of the detected antigen to the amount of a second antigen is known in the art. Nozawa teaches the motivation for use of such quantification methods by describing many of the problems that may

occur when attempting to associate the detection of an antigen with a disease state (see col. 1, line 32 – col. 3, line 39).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
July 12, 2004

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER